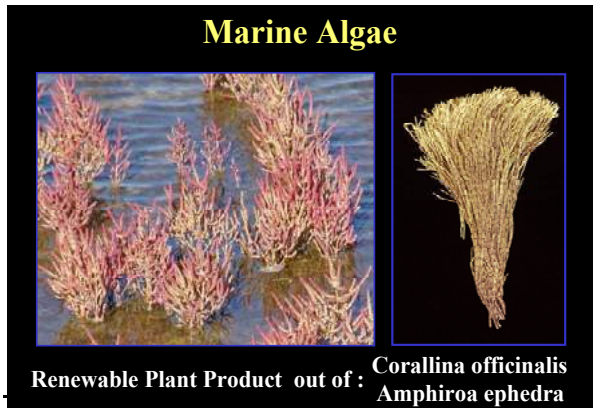
algisorb Brochure

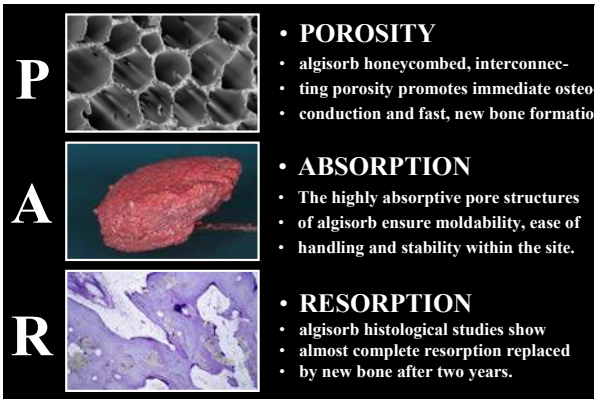


AligiPore® is a CE-certified product sold in Europe by Dentsply Friadent Gmbh since 1987. The same material was marketed in the U.S. by The Clinician's Preference and later by Scionx as C GRAFT™ which was cleared for marketing by the FDA in 2004. By now it is sold by Osseous Technology of America OTA (http://www.osseoustech.com) under the name **algisorb**.

All three brand names, AligiPore®, C GRAFT™ and **algisorb**, are a natural product synthesized from Corallina officinalis and Amphiroa ephedra, which is more simply, a renewable marine red algae.

Hundreds of years ago, this algae was classified by scientists as a plant. However, as the algae are incrusted through the calcium carbonate substance, they had to be reclassified as "Corallina algae". The name Corallina simply means "hard substance" and has nothing to do with **corals (**Corals are animals that sweat out calcium carbonate, which is a very solid, non porous form of calcium carbonate.) In all plants, water is transported by the capillary system. Therefore, these algae skeletons which are originally plants, provide a similar capillary system and an interconnecting micro porous matrix.

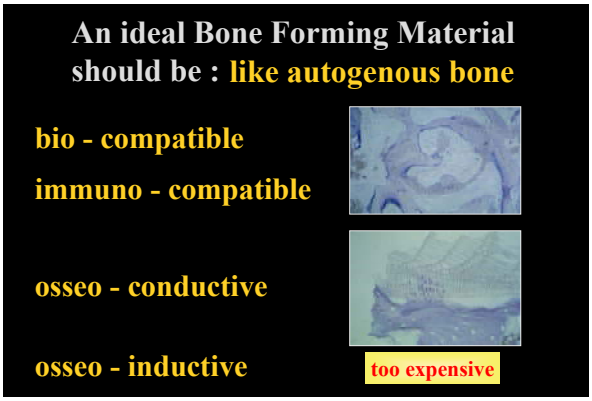
The three main advantages of **algisorb** are symbolised by the letters: **P**, **A,** and **R**.



P for Porosity: **algisorb** has a honeycomb like interconnecting porosity which provides for efficient osteoconduction and fast, new bone formation.

A for Absorption: The high absorptive pore structure of **algisorb** guarantees moldability, ease of handling and stability within the site.

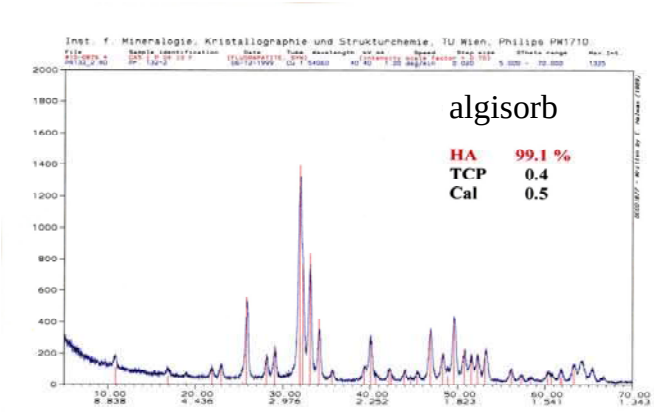
R for Resorption: Histological studies of **algisorb** (Ewers et al. 1987, Ewers and Schumann 1994, Schopper et al. 2003) report almost total resorption of the material with simultaneously substitution by new bone in 2 to 3 years. This process is commonly known as creeping substitution.



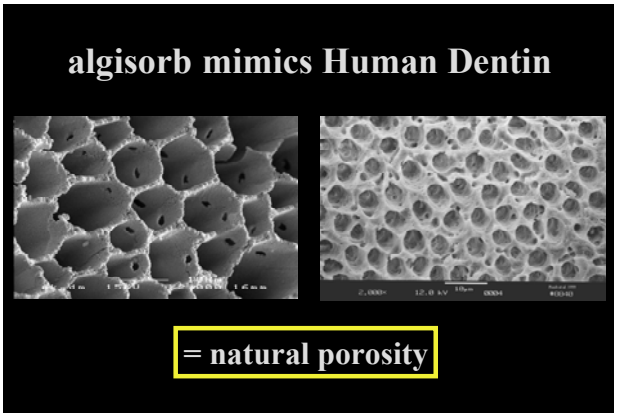
Bone grafting materials should always attempt to imitate the properties of autogenous bone. Therefore, the best choice is a natural product that is both biocompatible and immuno-compatible as well as osteoconductive. Unfortunately, there are no reasonable priced osteoinductive materials presently on the market.

algisorb has the following material specifications:

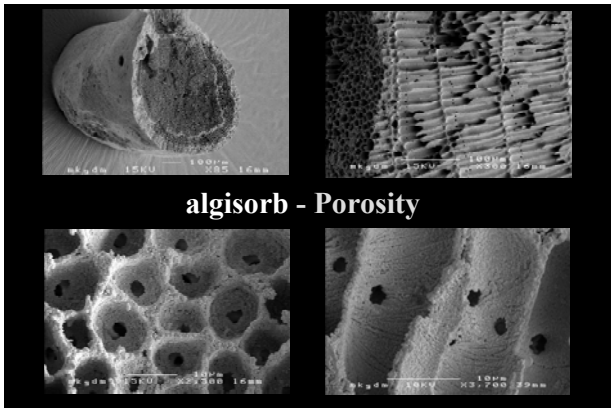
A natural product deproteinized by pyrolysis. During this processing, the algae bushel (stems) fall into granules and the organic material is changed from calcium carbonate into hydroxylapatite (Simon 1987, Spassova- Tzekova 2004).



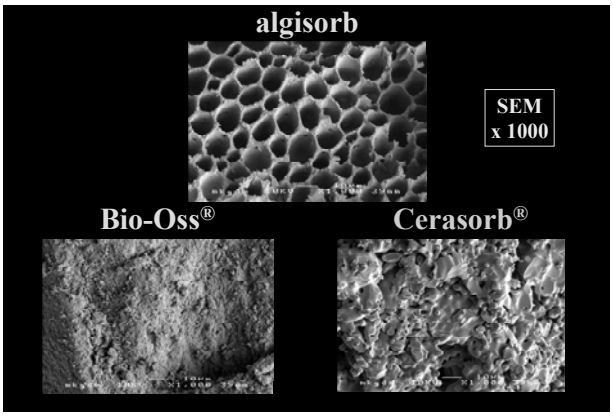
Routine checks are performed during processing by means of x-ray diffractometry at the Institute for Mineralogy, Crystallography and Structure Chemistry of the University of Vienna. A typical x-ray diffractogram of **algisorb**. This is now a fine, crystalline monophasic product with a minimum of 98 % apatite phase.



Porosity: The natural porosity of **algisorb** maybe compared with the honeycomb like structure of human dentin. The tubuli are twice as large as in human dentin.



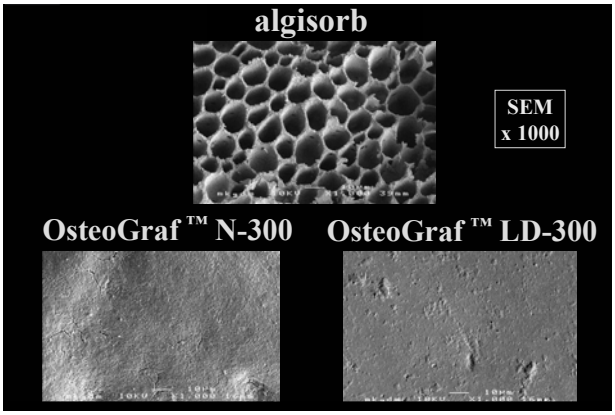
Here, the obvious porosity of **algisorb** is seen. The upper left shows a half granule. Note the outer cortex has a slightly less porosity than the inside structures which can be compared to cortical and spongy bone. The right side is a combination of a cross and longitudinal section which shows the 30 µm long tubuli with it's connecting perforations to the other tubuli. Note the connection of the tubuli always shows a central 1 to 3 µm wide perforation in the middle shown which is shown in the lower left picture. The tubuli themselves have lateral perforations as shown in the lower right picture. The central perforations can be compared to "Haversian Canals" and the lateral perforations with "Volkmann's Canals". The areas at the point of connection of the tubuli will have the most hydroxylapatite material. Therefore, these parts will demonstrate the slowest resorption making the **algisorb** bodies look like a ladder during resorption.



These SEM's demonstrate the obvious different porosity of competing materials at 1,000 magnification.

Bio-Oss®**:** Possess only nano porosity and shows no porosity in the dimension at 1,000 magnification.

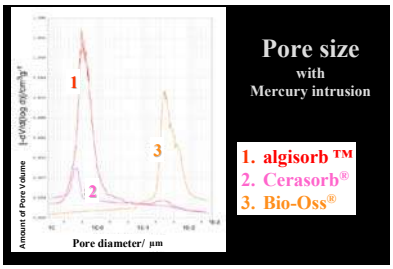
Cerasorb®**:** Superficial, non interconnecting pores which do not go into the deeper layers inside the particle.

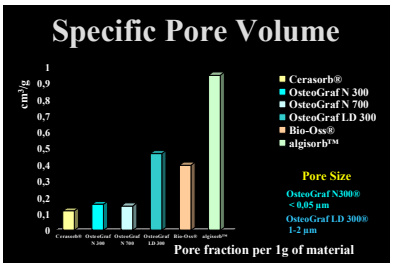


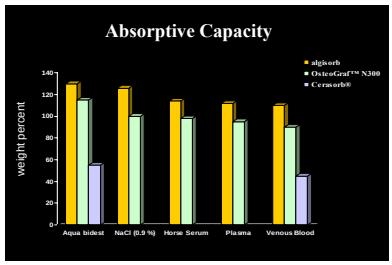
OsteoGraf® N-300 and OsteoGraf® LD-300: Minimal or no porosity is seen at 1,000 magnification.

algisorb demonstrates not only a surface porosity like Cerasorb but an interconnecting porosity through and through the particle into the deepest layers. Porosity is often measured by the amount of mercury or gas absorbed by the particle. Therefore, competitor products can claim porosity even though there is a minimal amount, or the pores themselves are in the nano dimension (Bio-Oss® pores are 10 times smaller than those in **algisorb**). This is misleading

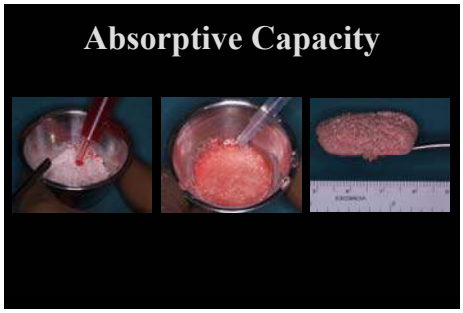
when discussing porosity since the nano dimension of porosity is not relevant for the biological process during new bone formation in the human body.



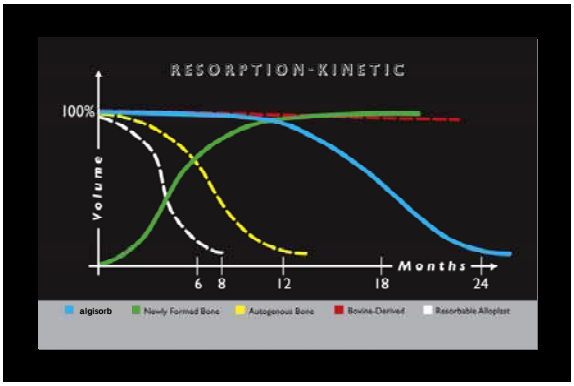




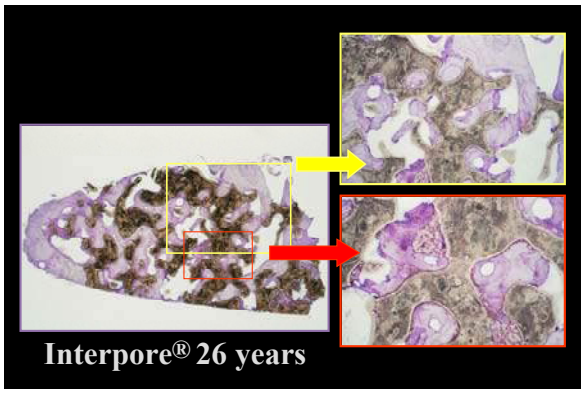
These 3 figures are direct comparisons of the specific pore volume illustrating a significant difference between the various brands with obvious superiority of **algisorb** with regards to specific surface and absorptive capacity.



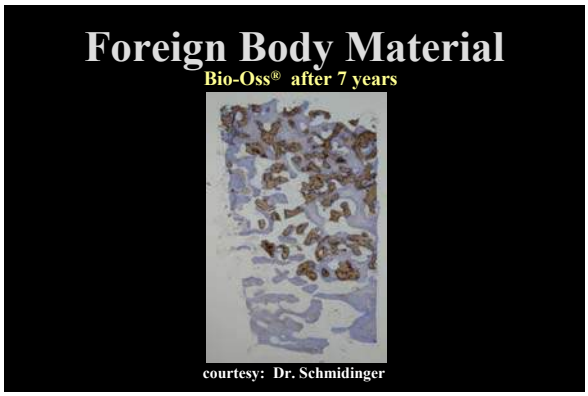
In clinical use, it is easy to observe absorption of biological fluids such as blood, PRP, proteins and / or peptides. With them **algisorb** can easily form a mouldable, cohesive body for ease of handling and placement into bony defects.



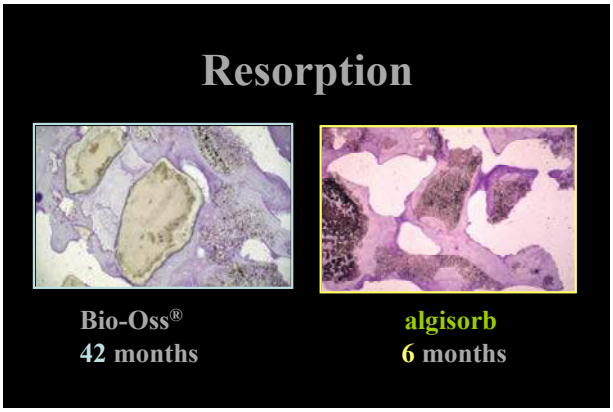
Resorption: **algisorb** is unique when compared to other materials in resorption kinetics. **algisorb** shows a high resorption rate starting within 12 months and is almost completely resorbed after two to three years (Ewers et al. 1998). However, the first 12 months are very important since during this time most of the volume of the material should not be resorbed or should not have major loss of volume. This is a typical characteristic of autogenous bone as well as fast resorbable alloplastic materials like TCP. Bovine materials however, will never resorb. Therefore, they remain in the body like a sequester or as foreign body material (Merten et al. 2003).



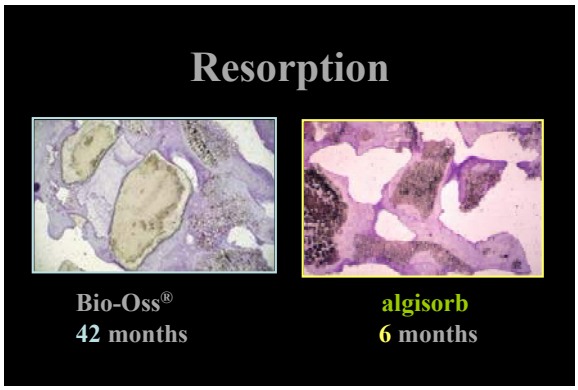
A histological preparation of Interpore®, coral bone grafting material previously distributed by Interpore Cross International. After 26 years, an excellent new bone formation is recognizable around the particulate material. However, even after 26 years this material shows no resorption or physiological adaptation at all. These results are similar to those observed with bovine products, such as Bio-Oss® (Merten et al. 2003).



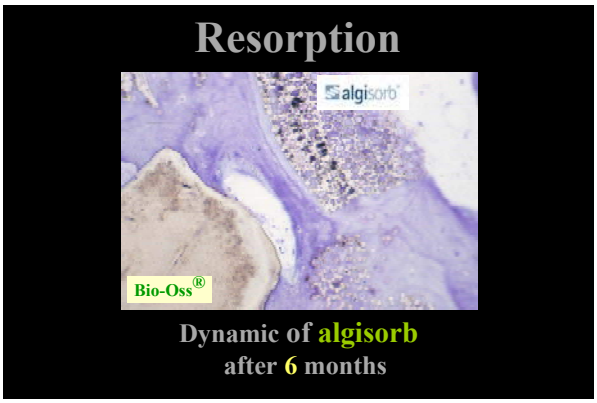
This histology provided by Dr. Schmidinger was taken after 7 years. There are no signs of resorption and no biodynamic bone remodelling of the bovinederived Bio-Oss® product.



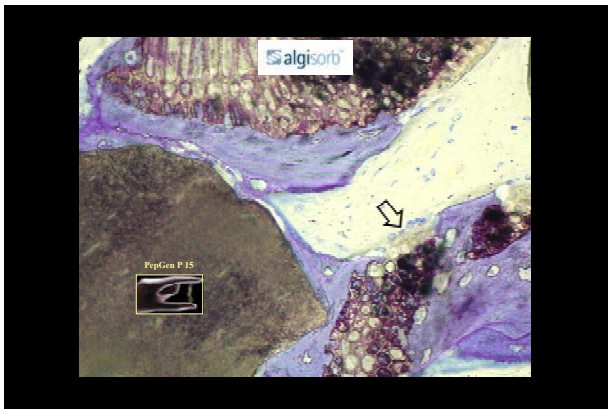
In a paper comparing Bio-Oss® with **algisorb**, Ewers et al. (2004) Bio-Oss® was used for a sinus grafting procedure with placement of 3 endosseous implants. 36 months after grafting, all 3 implants were lost and a second sinus graft was necessary. The re-graft was done with **algisorb** and new implants were placed 6 months later. The histological picture is of the original Bio-Oss® graft after 42 months and **algisorb** after only 6 months healing time.



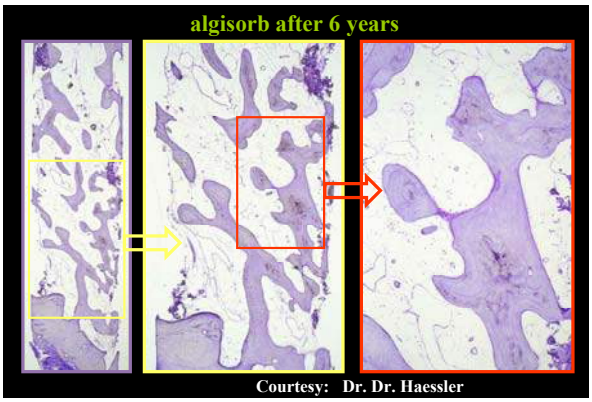
After 42 months of healing, Bio-Oss® demonstrates good osseointegration but without any bio-dynamic processes such as resorption or remodelling. In contrast, the **algisorb** granules, are incorporated into the bone after only 6 months showing the beginning resorption of some particles. Only in **algisorb** granules will new bone be evident inside the pore structures.



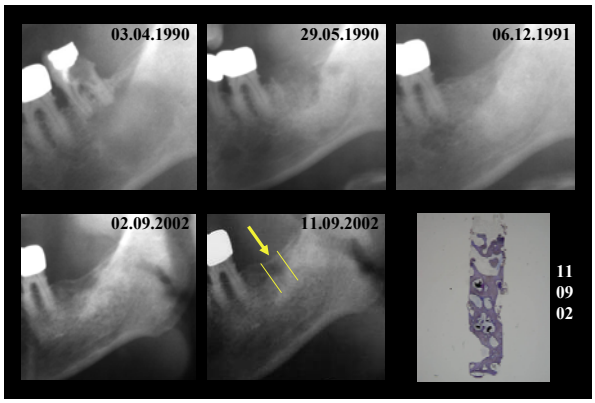
Another direct comparison shows the non-porous, highly sintered Bio-Oss® ceramic bodies on the left. On the right side, two **algisorb** granules, are completely surrounded by bone as well as filled with bone in the internal honeycomb structure. The **algisorb** granules are showing the beginning of resorption.



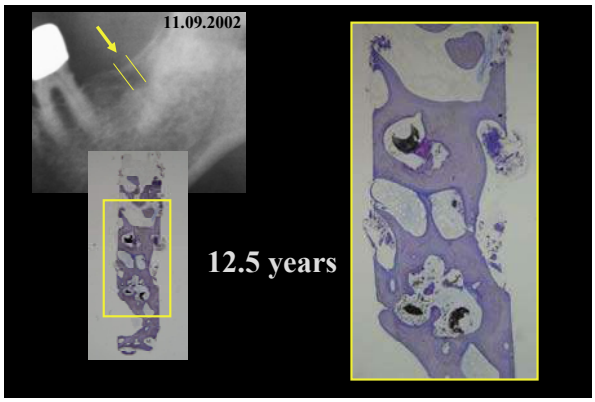
PepGen™P-15 (OsteoGraf™ N-300 combined with a synthetic peptide P-15, Dentsply Friadent CeraMed, Lakewood, CO) shows a circular icing of the PepGen P-15 material by bone without any signs of bio-dynamic processes. In a direct comparison to the **algisorb** granules, the particles are not only surrounded by bone but also filled with new bone after 5 months healing time. The black arrow points directly to an osteoclast lacuna which is covered on the outside by a cellular row of osteoblasts.



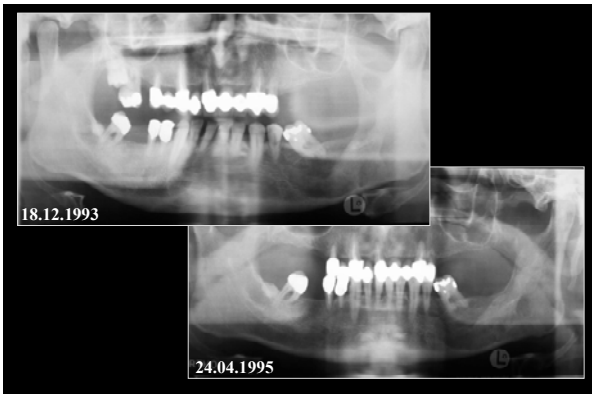
Dr. Haessler provides this histological picture of a 6 years from a sinus graft with **algisorb** material. At low magnification, just a few **algisorb** remnants remain. In the higher magnification, only 1 - 2 % remnant material remains.



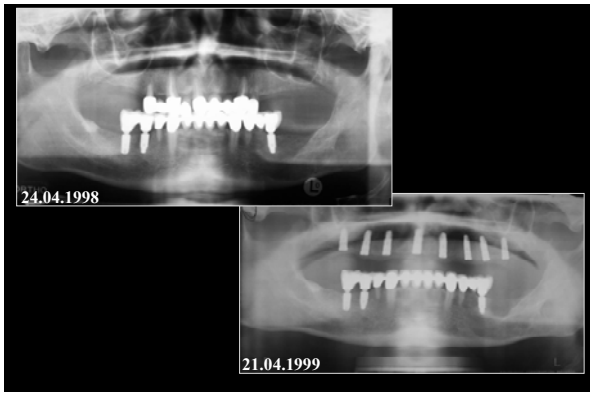
A 55 year old patient had a radicular cyst in combination with tooth 18. A surgical procedure was performed May 29th 1990. The immediate postoperative x-ray shows complete filling of the cyst cavity and extraction site defect with **algisorb**. Six months later excellent incorporation of the augmentation material and the ridge preservation can be seen. In September 2002, an x-ray shows the excellent incorporation of the augmentation material with newly formed bone. A 12 ½ year histological specimen was also taken at that time.



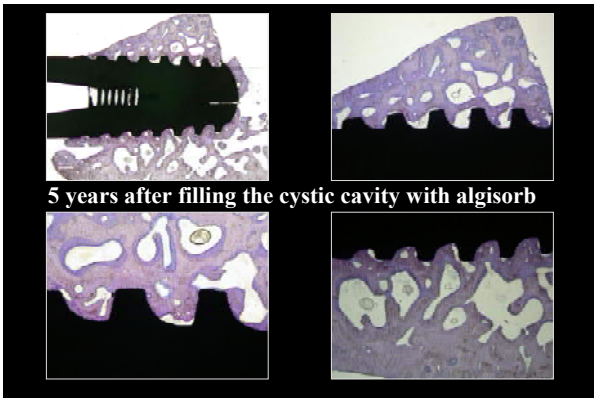
Only in the larger magnification of the marrow region are minimal remnants of **algisorb** seen with evidence of bone in different maturation stages.



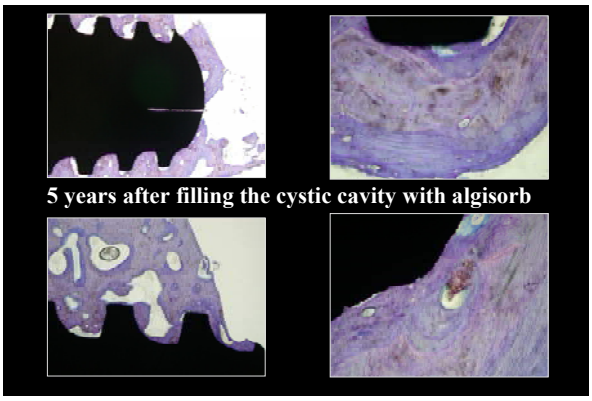
A 64 year old male patient had a keratocystic odontogenic tumor of the left mandible, starting distal of the second premolar up into the ascending ramus and just below the muscle process. In December 1993 the keratocystic odontogenic tumor was treated with Carnoy's solution and removed. The defect was filled with **algisorb**. An x-ray taken in 1995 shows the former defect completely filled with new bone. Only in the mandibular angle there is a small cystic defect.



In 1998, the patient received an implant but no core was taken at that time. In April 1999, a recurrence of the keratocystic odontogenic tumor was observed which involved the distal part of the implant. A block resection, including the implant, was performed and a resection osteosynthesis plate to stabilize the mandible was placed.

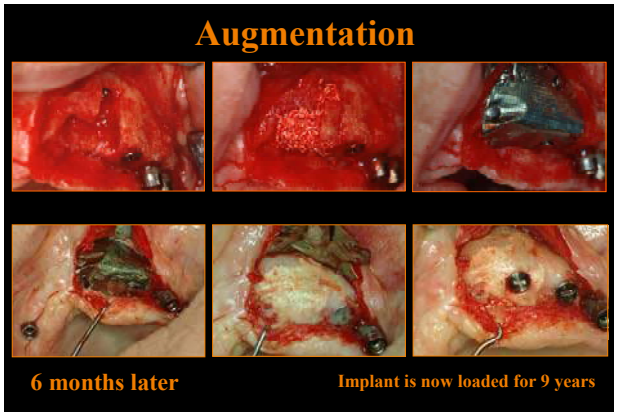


The histological preparation of the implant and the surrounding bone shows excellent osseointegration of the implant in the bone region that had been grafted with **algisorb**. In the low magnification only small remnants of **algisorb** are recognized.

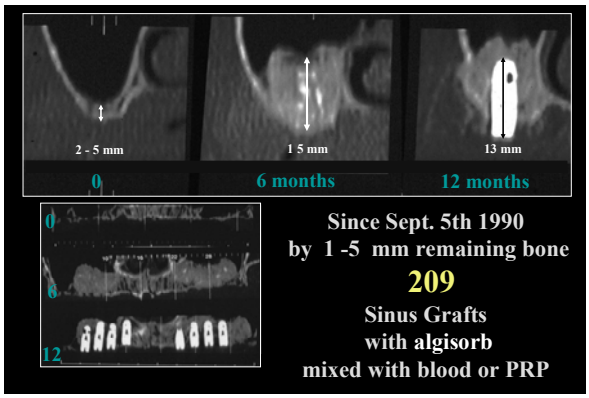


In a higher magnification, only minimal remnants of **algisorb** are shown as unresorbed fragments.

Indication and clinical results:

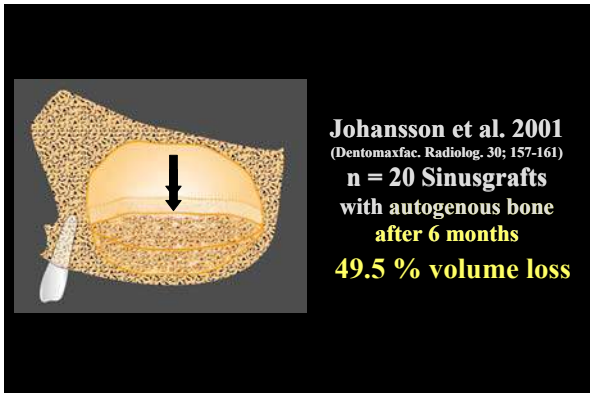


algisorb is suitable as an augmentation graft material. This situation shows the left quadrant of a maxilla with a huge bonydefect after the loss of 2 implants. The defect was filled with a small autogenous bone block and **algisorb** that was mixed with blood. The augmented defect was covered with a titanium membrane (Dentsply Friadent Gmbh, Germany). Six months later, the titanium membrane was removed and the augmented area was completely covered by new bone. Some **algisorb** bodies are noted shining through the bone. Only partial resorption can be expected in this short time period. An endosseous implant was placed which integrated well and has been loaded until now since 9 years.

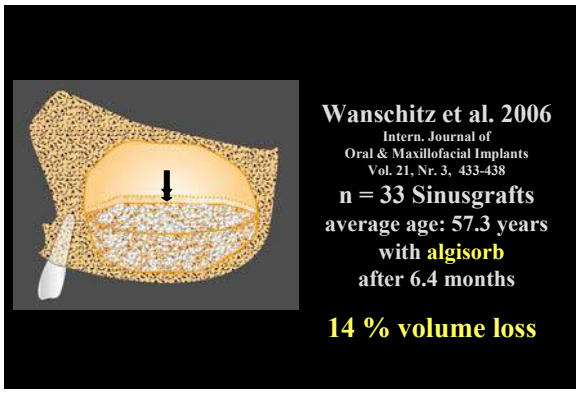


One of the main indications for use of **algisorb** is the sinus elevation procedure. Since September 1990, the author has performed 209 sinus grafts on 118 patients. This is a typical situation with approximately 1 mm of remaining bone. The piriform recess was filled with **algisorb** and after 6 months an increase of 15mm of bone height is seen. Prior to placement of a 13mm implant, a bone core is harvested for histological analysis. After an additional 6 months (total of 12 months post graft), the implant is uncovered and loaded. The Dental CT

panoramic pictures show almost no bone prior to the graft, the increased height of bone after 6 months, and the final picture shows the site after placement of 8 implants.



Although autogenous bone is often considered the Gold Standard, in 2001 Johansson et al. published a volume loss after sinus grafts with autogenous bone from the iliac crest of 49.5 % after 6 months healing time. A similar loss of volume was reported by Schlegel et al. in 2003.

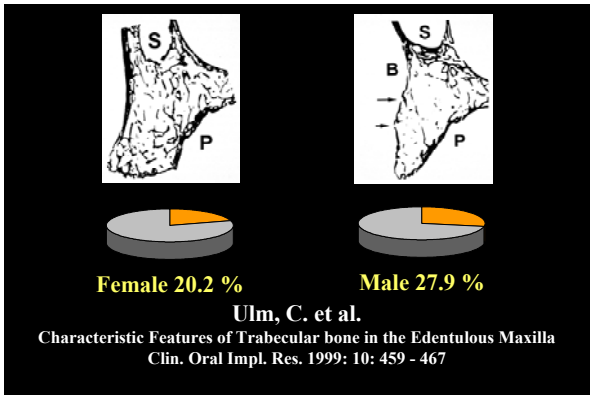


In 2006, Wanschitz et al. reported an average volume loss of 14 %. These results were from his investigation at 6.4 months on 33 sinus grafts done with **algisorb** with a mean patient age of 57.3 years. Between September 1990 and September 2004 (14 years), the author (Ewers 2005) performed 209 sinus graft augmentations on 118 patients utilizing **algisorb.** (The patient population included smokers and women over 50 years of age) (Ewers 2005)

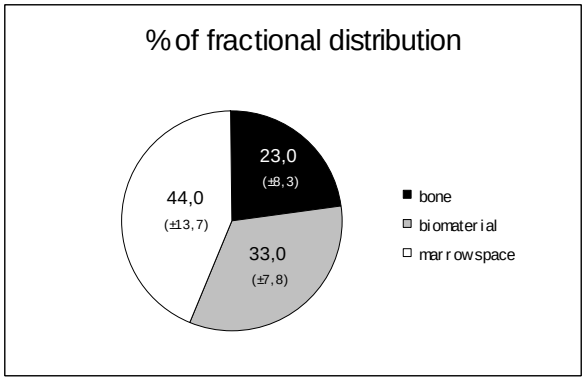
1. 614 implants were placed after 6 months of primary healing
2. The implants were loaded at 6 months post-graft
3. Only 27 implants (4.4%) were lost in this 156 month period

4. Implant survival rate of 95.6%

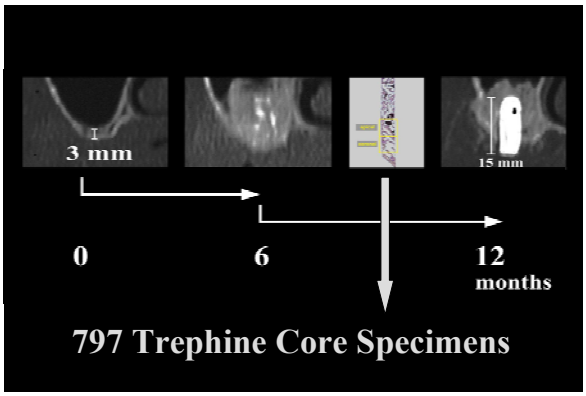
Literature surveys have reported a much lower implant survival rate, especially if autogenous iliac crest bone was used. The numbers are varying between 61.2% after 5 years (Kahnberg et al. 2001) down to 54.5% after 10 years (Kupfermann and Moy 2003). Other authors have reported similar survival rates (Keller et al. 1999, Pinholt 2003, Simion et al. 2004). If autogenous bone is mixed with xenograft augmentation materials, reports claim higher survival rates (Rosen et al. 1999, Hatano et al. 2004, Toffler 2004).



In 1999, Ulm et al. published that in the non-atrophied premolar and molar regions of the maxilla, women show 20.2% and men in average 27.9% bone.



In 2003, Schopper et al. showed 69 trephine histologies from 26 patients after 7 months healing time from sinus grafts with **algisorb.** They calculated 23 % new bone with 33% non resorbed material.

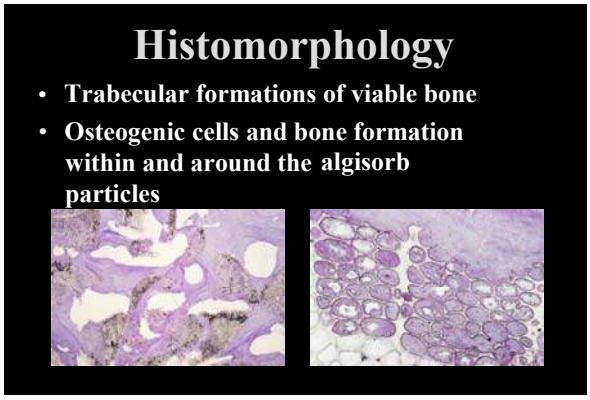


To obtain these histologies, cores of bone are harvested before the implants are placed. The cores are then prepared according to the method of Donath (1988) into non decalcified hard grinding sections and stained with Thionin.

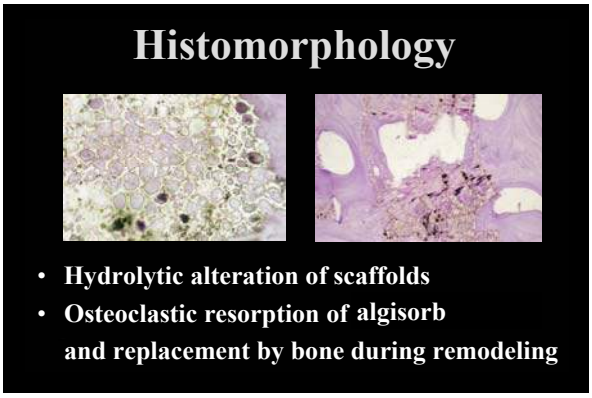
Following are several examples from the 797 human histology specimens that have been retrieved.

2 x magnification of histology from a 48 year old man after 8 months healing time. The graft consisted of 90% **algisorb** and 10% autogenous bone that was harvested during the surgery in a bone trap.

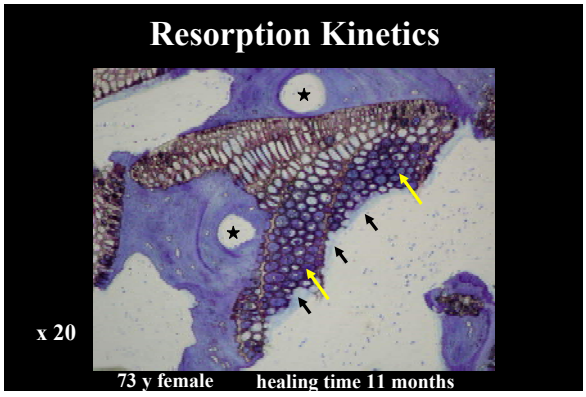
Schopper et al. reported (2003) the following observations:



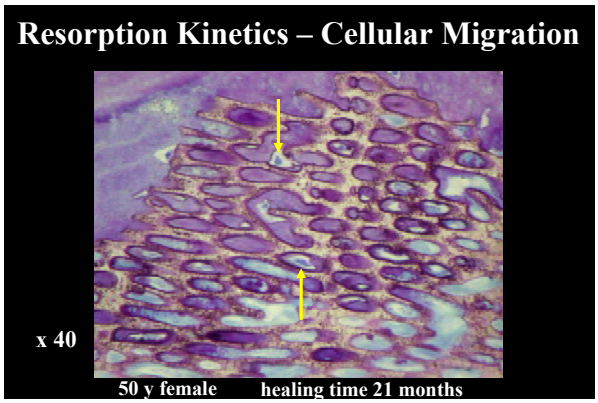
The histological evaluation shows trabecular formation with newly formed bone, osteogenetic cells and new bone formation in between and around the **algisorb** granules**.**



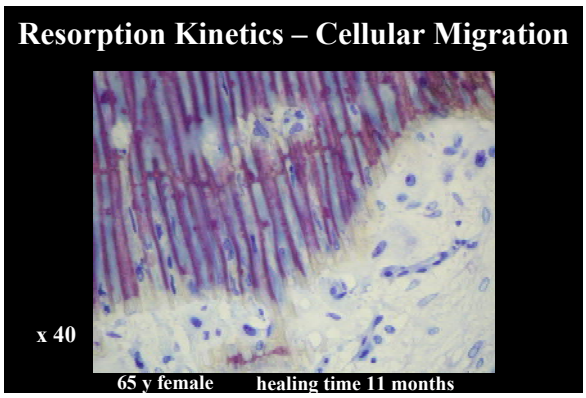
Hydrolytic alterations of the bone forming material were found as well as osteoclastic resorption of **algisorb** with continuous replacement of the biomaterial through the newly formed bone during the physiological bone remodelling phase. This process is known as "Creeping Bone Substitution".



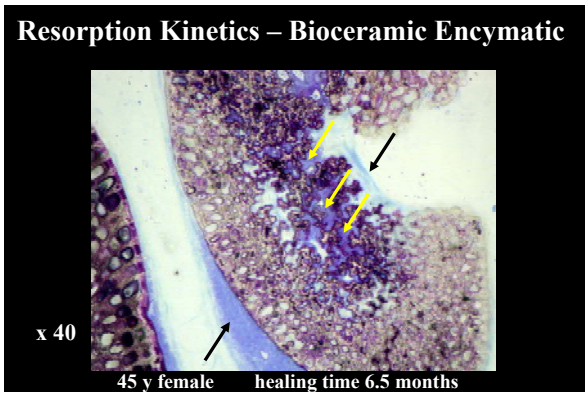
A 20 x magnification shows the histology of **algisorb** from an augmentation on a 73 years old lady with 11 months healing time. The **algisorb** granule is partly resorbed and the pores are filled with new bone. The 2 asterisks identify 2 osteones. In the lower portion of the slide, the hydroxylapatite body is being resorbed (black arrows) and the pores are already filled with new bone (yellow arrows).



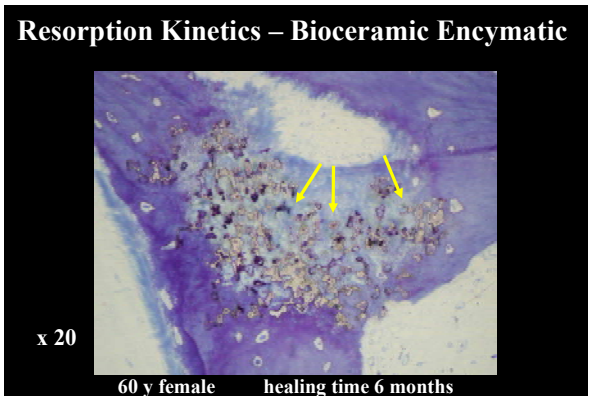
Note the cellular migration in this histological specimen from a 50 years old lady after 21 months healing time. The pores of **algisorb** are almost completely filled with osteoid or newly formed bone with numerous vital cells in between the pores (yellow arrows).



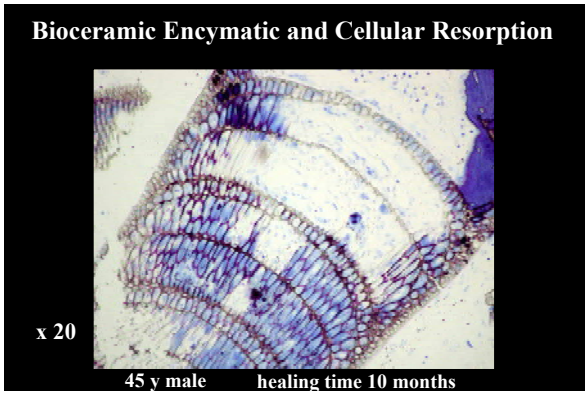
A 40 x magnification shows the cellular migration in a specimen from a 65 years old lady after 11 months healing time. Many tubuli are filled with living cells and the **algisorb** is resorbing either enzymatically or in an osteoclastic process.



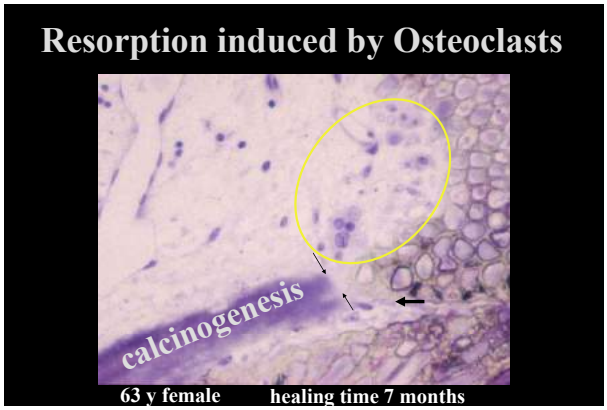
This figure shows the enzymatic resorption of the graft from a 45 years old lady with 6 ½ months healing time. The granule is partially dissolved enzymatically and replaced by new bone. The yellow arrows identify the maturing bone and the black arrows (on the right side and lower left side) show the new formed osteoid seam.



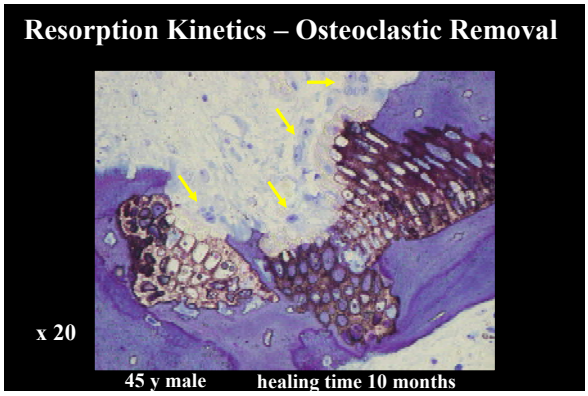
The 20 x magnification of the histology from a 60 years old lady with 6 months healing time shows almost complete enzymatic dissolution of the granule. Note the many pores that are filled with osteoid and maturing bone. The yellow arrows identify the numerous vital osteocytes.



After 10 months healing time of a graft in a 45 year old male, the resorption kinetics through enzymatic, as well as cellular dissolution or resorption, are clarified. The tubuli is partly resorbed. The connecting parts between the tubuli are more slowly resorbed since there is more hydroxylapatite at these points. Many pores are filled with osteoid and numerous vital cells surround the remaining hydroxylapatite material. The faster resorption of the tubuli combined with the slower resorption of the connecting parts between the tubuli, create a ladder like structure.

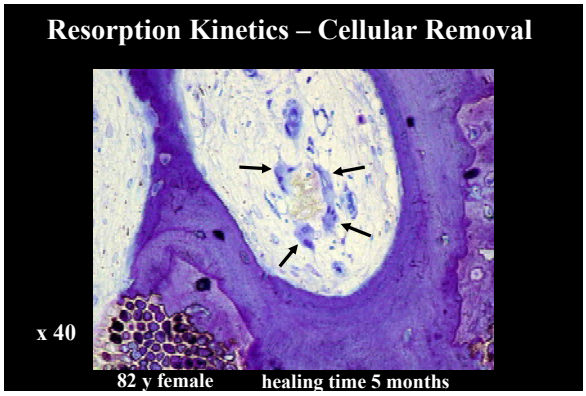


The histology from a 63 years old lady after 7 months healing time shows the resorption of the graft material and the new bone formation induced through osteoclastic activity. The osteoclasts have formed a large lacuna noted in the yellow circle. The big black arrow indicate the collagen fibres, which precede the calcinogenesis. The borderline in between these structures is marked with two small black arrows.

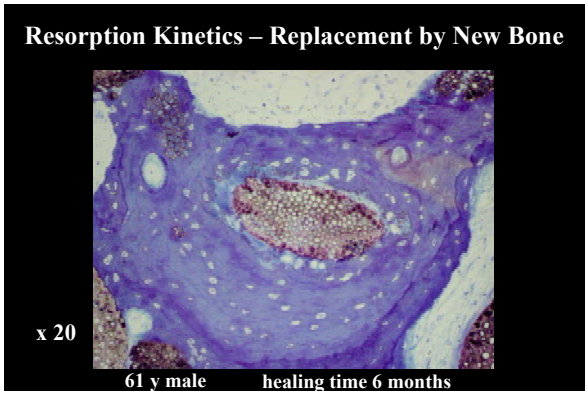


The histology from a 45 year male with a graft healing time of 10 months clearly shows the dissolution of the hydroxylapatite material due to osteoclasts and the parallel filling of the

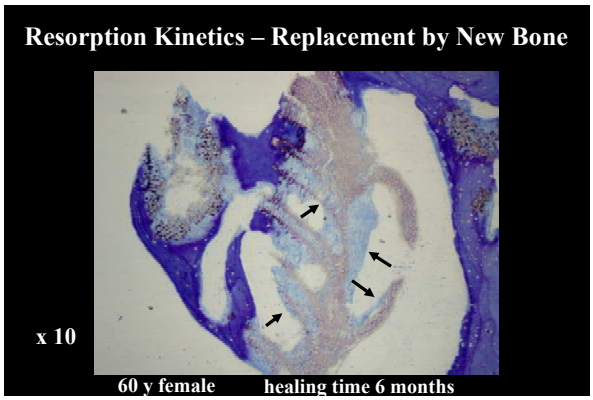
pores with bone (resorption is mainly induced by osteoclasts). The granule is surrounded by new bone and the pores are filled with new bone. In the large lacuna, which was carved by osteoclasts (yellow arrows) it is evident to see how the osteoclasts work on the hydroxylapatite material. The black arrows point to the osteoclastic resorption of the newly formed bone as well as demonstrating the normal remodelling process of human bone.



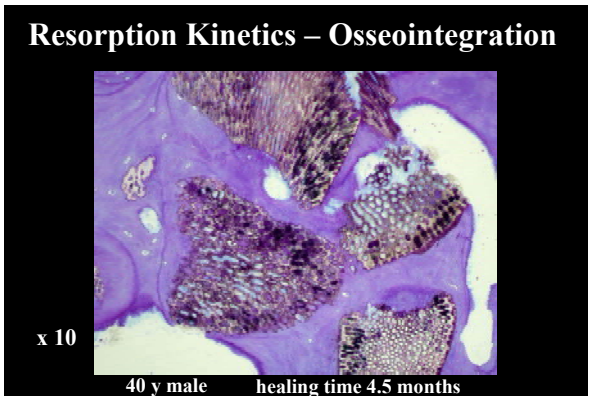
The histology from an 82 years old lady with 5 months healing time demonstrates the surprisingly high turn over of bone remodelling in spite of her age. Small remnants of **algisorb** granules are seen in the middle of the specimen but are surrounded by resorbing cells. All the other fragments are completely surrounded by new bone and the pores are also filled with new bone. Numerous vital osteocytes can be seen inside the maturing bone.



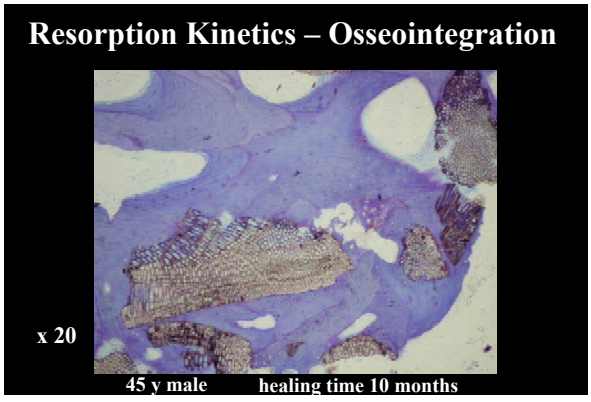
This Figure shows the 6 month histology from a 61 years old male. The granule is completely surrounded by newly forming bone which has also grown into part of the granule. Vital osteocytes can be seen within the new bone formation.



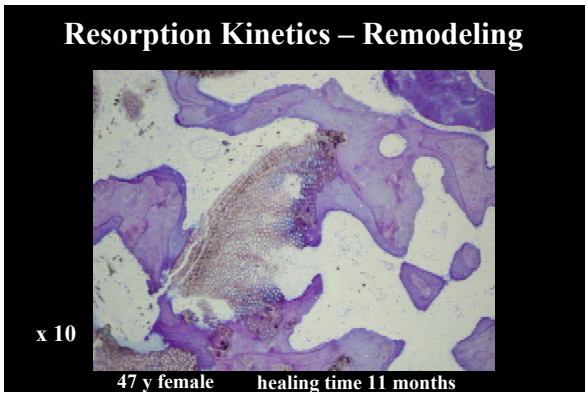
The histology from a 6 month core, taken from a 60 year old lady, shows new forming bone symbolized by the light blue osteoid seam. These seams of osteoid always grow along the hydroxylapatite material and are an excellent sign of the osteoconductive activity. The other side reveals the beginning changes of the maturing bone in the darker blue areas.



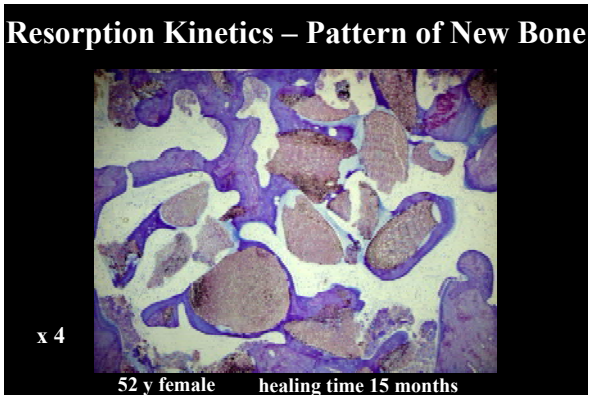
This is a pronounced example of osseointegration of the **algisorb** material in a specimen from a 40 year old male after 4 ½ months healing time. All pores are filled with osteoid and maturing bone and vital osteocytes are seen. This particular result was achieved with the addition of Platelet Rich Plasma (PRP).



Excellent osseointegration is shown in this histology taken from a 45 year old male after 10 months healing time. All granules are complete surrounded by bone and many pores are also filled with new bone which will continue to undergo remodelling.

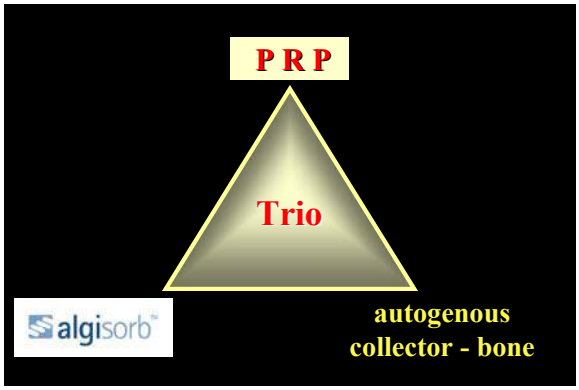


The histology from a 47 years old lady with 11 months healing time shows the trabecular architecture of the spongy structure with all stages of maturation of the newly formed bone. In the middle, the granule is partly filled with fresh osteoid or maturing bone. The surrounding of the granule by new bone underlay a continuous resorption pattern. The granule is involved in the dynamic process of new bone formation and resorption.

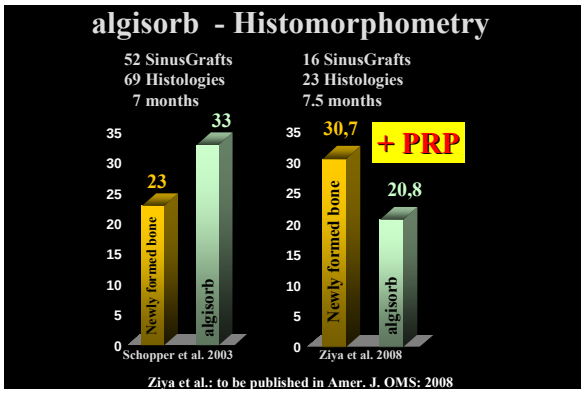


A 4 x magnification of the histology from a 52 years old lady with 15 months healing time, illustrates almost complete trabecular structure of the new formed bone due to the increased length of healing time. Most of the **algisorb** particles are surrounded by and interconnected by new bone, showing the conduction ability of this material and symbolizing the normal spongy structure of bone.

Using bone forming materials as spacers and scaffolds is ideal but the necessity for the presence of autogenous cells and stimulating (growth) factors must be considered.



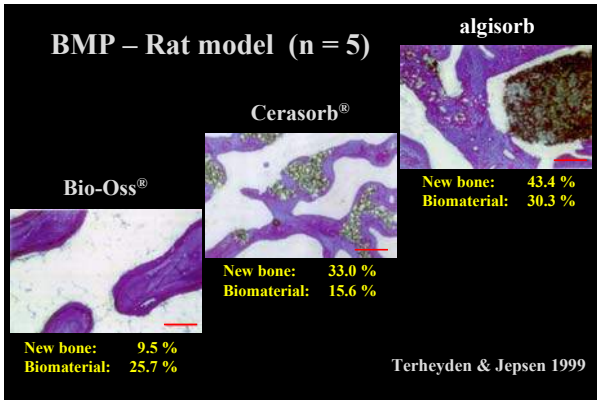
algisorb is a bone forming matrix and for the cellular component, autogenous or collector bone is used. The stimulator or growth factors commonly used, is the patient's blood. However, recent reports have confirmed the efficacy of PRP (Marx R.E. et. al. 1998). Ziya et al. (2006) investigated results with the use of PRP on 16 sinus grafts with 23 histologies, which were histomorphometrically evaluated.



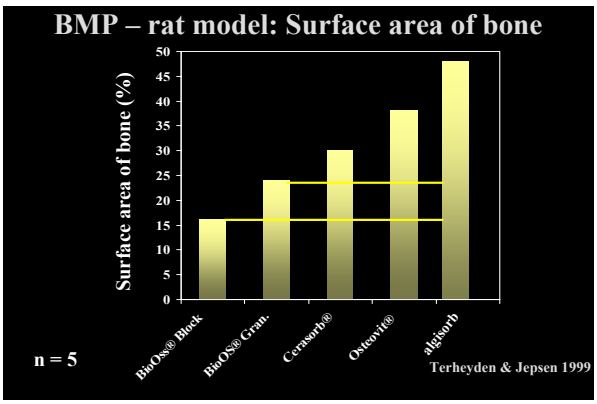
After an average healing time of 7 ½ months, it was found 31% new bone and only 21% of **algisorb** material remained in the graft site when PRP was used. Wiltfang et al. (2004) report on similar results by using Cerasorb®, a highly porous synthetic graft material. Other authors have reported poorer results in animal experiments. However, a non resorbing, highly sintered bovine material (Bio-Oss®) was used instead of the porous algae derived material (Fürst et al. 2003, Roldan and Terheyden 2004, Wiltfang et al. 2004)

Experimental investigations:

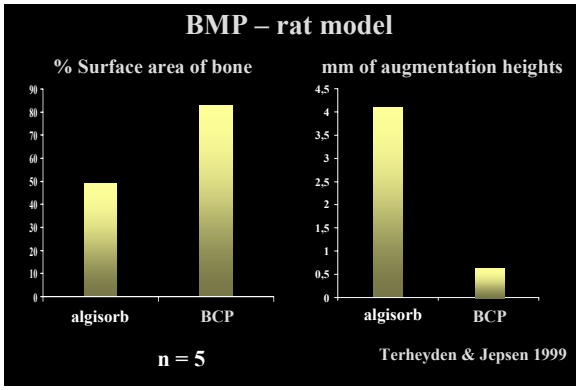
In 1999 Drs. Terheyden and Jepsen published their results with BMP experiments on rats in the Journal for Implantology.



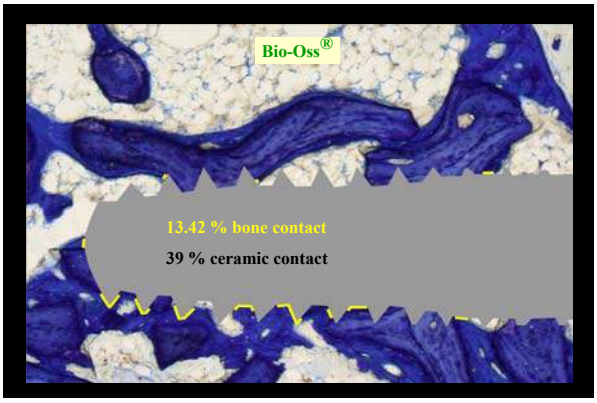
Although this publication mentions that Bio-Oss® had been the favored material in this experiment, the histomorphometric calculations were redone from their published pictures. The new findings revealed although the Bio-Oss® material is completely encapsulated by a thin layer of newly formed bone, histomorphometric analyse shows only 9.5 % bone and 25.7% residual biomaterial. Cerasorb® showed 33% new bone and just 15.6% remnant biomaterial. This is because the ceramic material resorbed too fast in this short time period and resulted in major volume loss. Comparing these results to those achieved with **algisorb** in the original paper that reported 43.4% new bone and 30.3% of remnant biomaterial, **algisorb** appears to be the logical choice as shown in the original histology pictures. **algisorb** demonstrated the highest amount of new bone with enough remnant biomaterial to maintain the augmented volume.



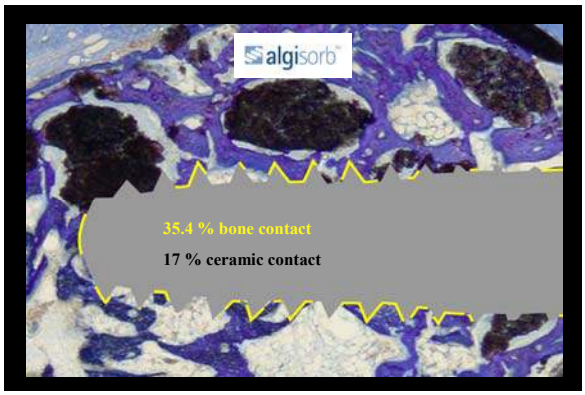
A diagram of the measured bone surfaces of all tested materials clearly shows the superiority of **algisorb** compared to Cerasorb® and Bio-Oss® granules
(BioOss® Blocks resulted in the least amount of bone).



In the experiments of Terheyden & Jepsen, the collagen preparation BCP showed the most bone surface histomorphometrically. However, the authors admitted the augmentation height achieved was only 1/8 of the augmentation height achieved with **algisorb**. This does show collagen to be the best carrier material for bone morphogenic protein (BMP) but collagen does not maintain the necessary volume and is therefore inferior when compared to **algisorb.** Similar results had been published by Hallmann et al. (2002).



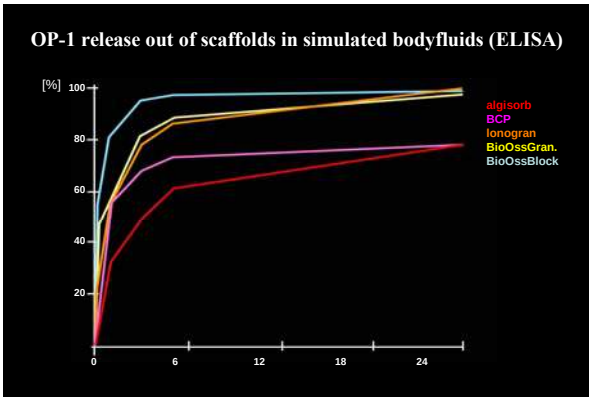
Simulating an implant placement into the original histology slide of Terheyden & Jepsen, the implant to newly formed bone contact in the Bio-Oss® graft is only 13.42%. The implant to highly sintered, non resorbable, non vital, foreign body material contact is 39.04%.



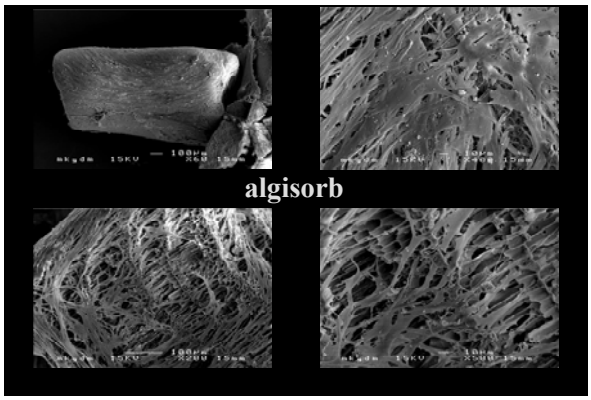
A simulated implant in the **algisorb** histology slide shows a 35.4% contact with newly formed bone and only 17.04% contact with the dynamic resorbing biomaterial. It should also be considered that this material will continue to resorb in future time. Increasing the new bone contact to the implant and decreasing the contact to algae material

Bio Tissue Engineering:

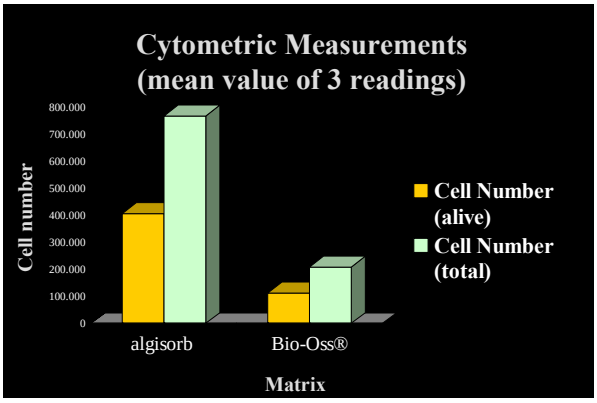
Bio-tissue-engineering experiments have always shown the advantages of **algisorb** due to the inter-connecting porosity and the high absorption capacity. In vitro experiments of Terheyden & Jepsen (1999) showed the release of rhOP-1 in artificial body fluid with different carrier materials. Measurements were taken using an ELISA-assay.



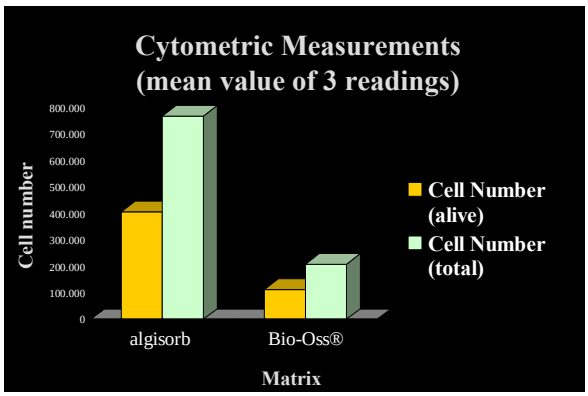
These experiments showed none of the materials tested could bind rhOP-1 tight enough, and after 24 hours, most of the applied material was dissolved. However, **algisorb** bound the rh-OP-1 material for the longest period of time.



On the left upper side, an **algisorb** granule is encapsulated with human osteoblasts after 12 days (Turhani et al. 2003). In the magnification, cell ramifications are seen growing into the tubuli.

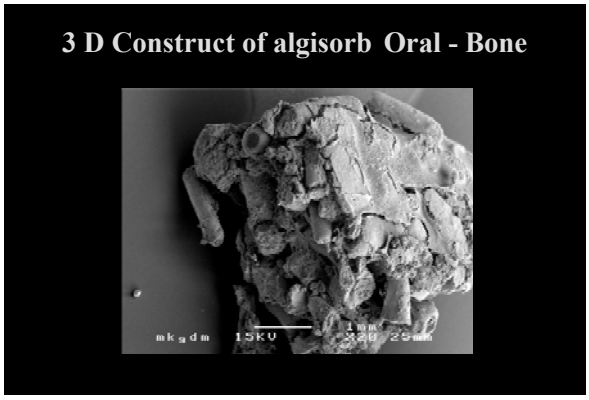


Cytometric measurements with 3x readings have shown **algisorb** having far more living cells and total cells (Turhani et al. 2004) than the bovine derived material.

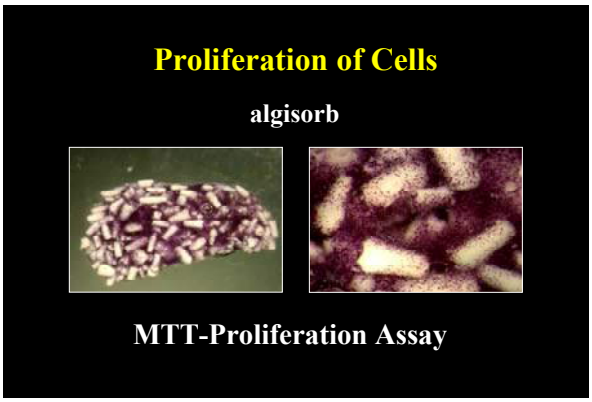


Measuring the difference between total cells and living cells is called the osseo conducting factor and **algisorb** proves to be superior to both Bio-Oss® and PepGen P-15.

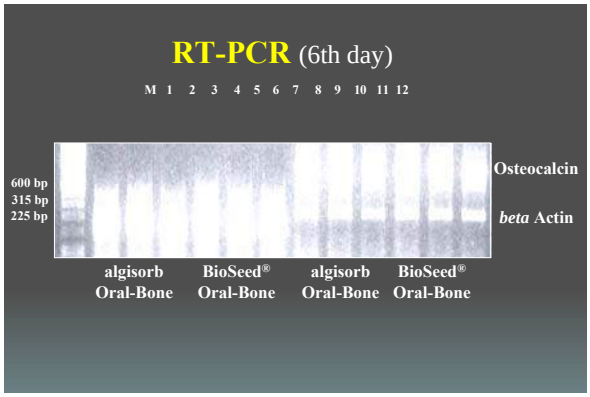
In 2005, Turhani et al. prepared cell-seeded 3-dimensional bone constucts using **algisorb** granules as carrier material and human osteoblasts in a “Rotating Wall Vessel” culture system.



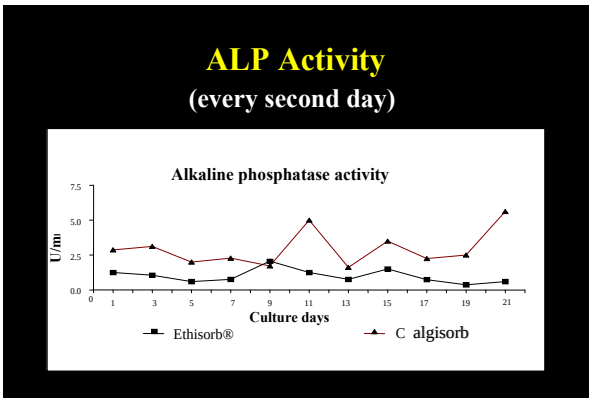
SEM analysis showed heavy growth and the presence of cell bridges between the **algisorb** granules.



Using the MTT proliferation tests, the vitality of the cells grown on **algisorb** granules could be demonstrated.



In a RT-PCR test, after 6 days **algisorb** show similar results as the 3-D convolute (Bioseed Oral Bone of the BioTissue Technologies Company, Freiburg im Breisgau, Germany).



Alkaline phosphatase was measured every second day until the 21st day. Remarkably higher activity was noted on **algisorb,** when compared to Oral Bone, which uses Ethisorb® as carrier material (Turhani et al. 2005).

This scientific demonstration was performed to report on the importance of the slogan **P A R**;

Porosity, **A**bsorption and **R**esorption.

These qualities, characteristics and requirements are met and surpassed by the material **algisorb.**

Due to the unique porosity, the high absorption capacity, the presence of an immense amount of cell chambers and the positive resorption kinetic (which allows for future biomechanical loading of the bone) we call **algisorb** a **true bone conducing and regenerative material**.

Acknowledgements:

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